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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NC.	CONFIRMATION NO.
10/054,678	01/22/2002	Pamela Sklar	2825.2012-004	4000

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EXAMINER	
MYERS, CARLA J	

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 07/30/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/054,678	SKLAR ET AL.	
	Examiner	Art Unit	
	Carla Myers	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 May 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,6-8,10-12 and 28-40* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3, 6-8, 10-12 and 28-40* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. This action is in response to the amendment filed May 17, 2004. Applicant's amendments and arguments have been fully considered but are not persuasive to overcome all grounds of rejection. All rejections not reiterated herein are hereby withdrawn. This action is made final.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3, 6-8, 10-12, 28-40 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods for determining whether an individual has an increased likelihood of having or developing bipolar disorder wherein the method comprises performing an inheritance study wherein an individual that is the offspring of a parent having bipolar disorder is analyzed for the inheritance of a haplotype consisting of an A at nucleotide position 476, a G at nucleotide position 942 and a C at nucleotide position 1635 of the dopamine beta-hydroxylase gene (DBH) gene and wherein the inheritance of said haplotype is indicative of an increased likelihood that the individual will have or will develop bipolar disorder, does not reasonably provide enablement for methods of diagnosing bipolar disorder or assessing the likelihood of an increased or decreased symptomology in an individual by detecting any one of an A at nucleotide position 476, a G at nucleotide position 942 or a C at nucleotide position 1635 of the DBH gene as indicative of an increased likelihood that

said individual will have or will develop a bipolar disorder or as indicative of an increased or decreased symptomology of bipolar disorder The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The following factors have been considered in formulating this rejection (*In re Wands,* 858F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988): the breadth of the claims, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, the amount of direction or guidance presented, the presence or absence of working examples of the invention and the quantity of experimentation necessary.

The claims as amended are drawn to methods for diagnosing or aiding in the diagnosis of a bipolar disorder wherein the method comprises determining the nucleotide at any one or more of the positions 476, 942 or 1635 of the dopamine beta-hydroxylase gene wherein the presence of any one of an A at nucleotide position 476, a G at nucleotide position 942 or a C at nucleotide position 1635 of the DBH gene is indicative of an increased likelihood that said individual has or will develop a neuropsychiatric disorder or wherein the presence of any one of a G at nucleotide position 476, a T at nucleotide position 942 or a T at nucleotide position 1635 of the DBH gene as indicative of a decreased likelihood that said individual has or will develop a neuropsychiatric. The claims further include methods for assessing increased or decreased symptomology associated with a bipolar disorder by detecting two or more of the above DBH polymorphisms.

Case law has established that "(t)o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.'" *In re Wright* 990 F.2d 1557, 1561. *In re Fisher,* 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) it was determined that "(t)he scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art". The amount of guidance needed to enable the invention is related to the amount of knowledge in the art as well as the predictability in the art. Furthermore, the Court in *Genetech Inc. v Novo Nordisk* 42 USPQ2d 1001 held that "(I)t is the specification, not the knowledge of one skilled in the art that must supply the novel aspects of the invention in order to constitute adequate enablement". In the instant case, the state of the art of diagnosing a neuropsychiatric disorder by detecting a polymorphism is highly unpredictable and the specification has not provided sufficient guidance to enable the skilled artisan to practice the invention as it is broadly claimed for the reasons set forth below.

The specification (see, for example, page 7) provides the results of a study of the transmission of DBH polymorphisms to offspring diagnosed as having bipolar disorder. The study found that the haplotype consisting of an A at nucleotide position 476, a G at nucleotide position 942 and a C at nucleotide position 1635 of the DBH gene was transmitted to offspring diagnosed as having bipolar disorder more often "than would be expected by chance." The specification (page 7) also states that "(t)hus it appears that the less common allele (the variant allele) of each of the three SNPs may contribute to protection or reduction in symptomology with respect to neuropsychiatric disorders,

while the more common allele (the reference allele) of each of the three SNPs may predispose an individual to a neuropsychiatric disorder or to increased symptomology of these disorders. The association is particularly strong when two or more of the alleles are considered in combination, and strongest when all three alleles are considered in combination." The transmission data set forth in Figure 2 shows that the p-value for transmission of the individual alleles was not significant. For example, in the first study, the 1635 polymorphism was transmitted to 28 offspring, but was not transmitted to 21 offspring, generating a p value of .4635; the 942 polymorphism was transmitted to 18 offspring, but was not transmitted to 12 offspring, generating a p value of .2733; and the 476 allele was transmitted to 56 offspring, but not to 41 offspring, generating a p-value of .1278. Variable results were obtained between 2 studies for transmission of pairs of haplotypes. For example, in one study the 1635 and 942 allele 1 polymorphisms transmitted in 37 individuals and not in 22 individuals, generating a p-value of .0508, whereas in a second study, this combination of alleles was transmitted to 18 individuals and not to 11 individuals, generating a p-value of .1936. Most importantly, the specification does not provide any information on the general occurrence of the haplotypes or individual alleles in the general population versus an affected population. There are no teachings in the specification as to how to apply the claimed method to the general population by detecting the haplotypes or single alleles in any individual as indicative of a bipolar disorder. As indicated in the specification, the alleles found to be associated with inheritance of bipolar disorder are the alleles that are the most prevalent in the general population. For example, Cubells (American Journal of Medical Genetics

(1997)) teaches that the DBH*304A allele (i.e., the alanine allele; referred to in the specification as the DBHu1 G allele) was the most common allele in all populations tested, with allele frequencies greater than 0.80. If one practiced the claimed invention as written, then one would conclude that at least 80%of the individuals in the general population had an increased likelihood of having a neuropsychiatric disorder. Such a finding is not consistent with the actual prevalence of these disorders in society. Cubells (see abstract) goes on to state that there is significant heterogeneity in the frequency of the allele across different populations and that this "demonstrates the importance of controlling for population stratification in future studies testing for associations between DBH*304S and clinical phenotypes." There are no specific teachings or examples in the specification of using the claimed methods to detect the occurrence or susceptibility to neuropsychiatric disorders in the general population by analyzing DBH nucleic acids from any member of the population for the occurrence of one or more of the DBH polymorphisms at positions 476, 942 or 1635. In view of the teachings of Cubells and the lack of information provided in the specification, it is highly unpredictable as to whether a method which detects the most prevalent form of each allele could be used to detect that allele as indicative of an individual having or being susceptible to developing a neuropsychiatric disorder.

Secondly, the specification does not teach an association between the level of symptomology of bipolar disease and the occurrence of the DBH alleles. There are no examples provided in the specification of a method in which an individual was assessed as having an increased or decreased symptomology of bipolar by detecting

two or more DBH alleles. Given the unpredictability in establishing an association between the DBH alleles and the occurrence of bipolar in the general population, it is further unpredictable as to whether the level of symptomology of bipolar disease would be associated with the DBH alleles.

Secondly, while the claims have been amended so that they are limited to methods for diagnosing bipolar disorder, the teachings in the art demonstrate the overall unpredictability in diagnosing neuropsychiatric disorders by detecting DBH alleles. For example, Kirov (Molecular Psychiatry (1999) 4: 558-565; see page 559, 561 and abstract) reports that the DBH*304A polymorphism (i.e., the DBHu1 polymorphism at position 942) was not found to be associated with transmission or occurrence of bipolar disorder. Further, Cubells (Molecular Psychiatry (2000) 5: 56-63) teaches that there was no significant differences between the frequency of the DBH*444g/a allele in healthy European Americans as compared with individuals in a cocaine-dependent group. Accordingly, Cubells essentially teaches that in the general population, the DBH*444 A allele (i.e., an A at nucleotide position 476) is not associated with risk of cocaine-dependency (i.e.., substance abuse or substance use). Cubells did find that the DBH*444g/a alleles were in linkage disequilibrium with DBH*5-ins-del alleles. At page 60, Cubells teaches that "(n)either DBH*5'-del or DBH*444a alone significantly associated with cocaine-induced paranoia, presumably because some of the alleles at each individual polymorphism occurred on different haplotypes backgrounds, and were therefore in weaker LD with low-DBH functional variants." Additionally, the cocaine-dependent group did not exhibit differences in DBH haplotype (DBH*5-ins/del and

DBH*444a/g) frequencies when compared to normal European Americans. However, when the cocaine-dependent group was divided into paranoia (+) and paranoia (-) individuals, it was found that the DBH*5 del / DBH*444 a haplotype was more prevalent in paranoia (+) versus paranoia (-) cocaine users. Accordingly, Cubells highlights the unpredictability of applying the claimed method to the general population and the unpredictability of determining susceptibility to neuropsychiatric disorders by analyzing a single DBH polymorphism. The unpredictability in the art is further emphasized by the teachings of Williams (American Journal of Medical Genetics (1999) 88:557-559). This reference teaches that the DBHu1 polymorphism is not associated with susceptibility to schizophrenia. Cubells (Society for Neuroscience Abstracts. November 2000. 26(1-2): page 1161, abstract 436.1) teaches that the while the DBH*444A (position 476) polymorphism is associated with lower plasma DBH levels, the polymorphism was not associated with unipolar psychotic depression. Houy et al. (American Journal of Human Genetics. August 2000. 96: 528, abstract P208) teaches that the Ala-304-Ser polymorphism (DBHu1 polymorphism at position 942) is not associated with deficit schizophrenia. Iwata (American Journal of Medical Genetics. January 2003. 116B:23-26) were also unable to find an association between the Ala-304-Ser polymorphism and early-onset schizophrenia. Additionally, Payton (American Journal of Medical Genetics (2001) 105: 464-470) reported that the DBHu1 polymorphism was not associated with attention-deficit hyperactivity disorder.

Accordingly, in view of the lack of specific guidance and teachings provided in the specification and in view of the unpredictability in the art, undue experimentation would be required to practice the methods as they are broadly claimed.

RESPONSE TO ARGUMENTS:

In the response filed May 17, 2004, Applicants traversed the 112, first paragraph rejection by stating that the specification provides "transmission/association data" for each of the SNPs individually and pairwise. However, the specification (Figure 2) provides only information regarding the transmission of the DBH alleles. The specification does not provide any information on the occurrence of these alleles in the general population of normal individuals and individuals having bipolar disorder (BP). Further, the data in Figure 2 highlights the unpredictability in the art of using only one or two of the alleles as a means for diagnosing bipolar disorders. For example, when the results of each study are taken alone, there does not appear to be a significant correlation between transmission of the individual alleles. In the first study, the 1635 polymorphism was transmitted to 28 offspring, but was not transmitted to 21 offspring, generating a p-value of .4635; the 942 polymorphism was transmitted to 18 offspring, but was not transmitted to 12 offspring, generating a p-value of .2733; and the 476 allele was transmitted to 56 offspring, but not to 41 offspring, generating a p-value of .1278. In the second study, the 1635 polymorphism was transmitted to 14 offspring, but was not transmitted to 8 offspring, generating a p-value of .2008; the 942 polymorphism was transmitted to 11 offspring, but was not transmitted to 13 offspring, generating a p-value of .6831; and the 476 allele was transmitted to 49 offspring, but not to 38 offspring,

generating a p-value of .2383. With respect to the transmission of pairs of haplotypes, variable results were obtained between the two studies. For example, in the first study the 1635 and 942 allele 1 polymorphisms transmitted in 37 individuals and not in 22 individuals, generating a p-value of .0508, whereas in a second study, this combination of alleles was transmitted to 18 individuals and not to 11 individuals, generating a p-value of .1936.

The unpredictability of diagnosing BP and assessing the level of symptomology of BP by analyzing DBH polymorphisms is also emphasized by the teachings of Kirov, as discussed above. Kirov teaches that the DBH*304A polymorphism (i.e., the DBHu1 polymorphism at position 942) was not found to be associated with transmission or occurrence of bipolar disorder. The reference (page 561) states that "Linkage studies have provided no evidence for linkage between BP and DBH...Our results do not provide evidence that this functional variant increases susceptibility to BP." In the response of May 17, 2004, Applicants state that the experimental method set forth in the present specification is "robust to non-random mating." However, Applicants do not provide evidence that their methodology can be used in place of association or linkage studies to determine whether an allele or combination of alleles is diagnostic of disease in the general population. It is maintained that the teachings in the specification are based only on transmission data and do not address the frequency of the alleles in the general population. There is no showing in the specification that the data obtained from transmission studies can be applied to the general population. As discussed above, the individual alleles used in the claimed methods to diagnose BP are the alleles found to

be the most prevalent alleles in the general population. Again, the 942 G allele is found in at least 80% of the population. There is no evidence to support a conclusion that 80% of the population is at an increased risk of having BP since BP does not occur at this frequency in the population. Accordingly, it is clear that one could not use the 942 allele alone to predictably determine whether an individual was at risk of having or developing BP. If the transmission data obtained for 942G is not sufficient to allow for the use of this allele to diagnose BP in the general population, why would the transmission data for the 476A allele alone or for the combination of alleles be sufficient to allow for the diagnosis of BP in the general population? Without information regarding the prevalence of the 476 and 1635 alleles in the general population, it is highly unpredictable as to whether these individual alleles or combinations of alleles could be used to diagnose BP or assess increased or decreased symptomology of BP. There is no evidence provided in the specification to support a conclusion that the presence of the 476A allele or the combination of two or more of the 476A, 942G or 1635C alleles can be used to diagnose the general population for an increased risk of having or developing BP.

It is stated that "Applicants have amended the claims to recite individuals who are symptomatic and/or at risk for the development of bipolar disorder." However, the phrase "at risk for development of bipolar disorder" is not defined in the specification as referring to any particular subgroup of the population. All members of the population have some level of risk of developing bipolar disorder. Thus, this recitation does not provide a meaningful limitation with respect to the population that is analyzed by the claimed method. Further, the amendment to include this limitation does not obviate the

need to provide information regarding the prevalence of the 476 allele or the combinations of the 476, 942 and 1635 alleles in individuals having BP versus controls. Nor does this amendment obviate the issues associated with the lack of information regarding an correlation between BP symptomology and the occurrence of 2 or more of the 476, 942 and 1635 DBH alleles.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carla Myers whose telephone number is (571) 272-0747. The examiner can normally be reached on Monday-Thursday from 6:30 AM-5:00 PM. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion, can be reached on (571)-272-0782.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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Carla Myers
July 27, 2004

Carla Myers
CARLA J. MYERS
PRIMARY EXAMINER